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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BALASUBRAMANIAN, VENKATARAMAN

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/21/2002 12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,320	HINZ ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of invention of Group XII in Paper No. 11, along with the election of species of example 6, is acknowledged. Claims 1-10 and 11-12 will be examined to the extent they embrace the elected subject matter.

Claims 1-10 and 12-13 are pending.

Applicants' traversal of restriction requirement is fully considered but deemed as not persuasive for reasons of record. As for the traversal, the following apply.

1. Contrary to applicants' urging, the invention does not have a special technical feature as it fails to meet both the requirement of unity of invention. As noted before unity of invention requires that a) compounds within the Markush group share a common utility and b) share a substantial structural feature essential for that utility. Both these requirements are to be met with not one or other.

   Principles of classification dictate that ring structures having different numbers of heteroatoms to be classified in different classes. Such classification, as noted in the previous office action, stems from the fact that the ring structures have different properties, different reactivities and different effects on the substituents. They are made and used differently. Thus the instant invention, which embraces different cores, fails to meet the first criteria of unity of invention. Furthermore, the core structures do not share the only recited utility as evident form the prior art cited in the International Search Report and the instant specification, which recite several other uses.

Hence the instant claims fail to meet both the requirements stated above. Furthermore, applicants have not asserted that the core groups are all equivalent. In which case, prior art which anticipates instant elected invention (such as those ten X references cited in the International Search Report) may then render the non-elected inventions as obvious variant and can thus be applied.

Applicants' attention is also drawn to PCT/ISA/210 Box I.2, which is reproduced here for the record.

Present claims 1-3,5-9,11 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Furthermore, the term "prodrugs" used in claims 1-4 is vague and unclear and leaves in doubt as to the meaning of the technical features (i. e. the compounds) to which it refers. The use of this term in the present context is considered to lead to lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in table 1, in the examples 44 to 58 in claim 4 and closely related homologous compounds such as mentioned in the description at page 22.

Claims searched completely: 4, 10

Claims searched incompletely: 1-3, 5-9, 11

The applicant's attention is drawn to the fact that claims or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an International preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any chapter II procedure.

2. As for classification issue raised by the applicants, in the restriction practice of a 371 of PCT application it is not essential to provide class/subclass classification.

3. Applicants are incorrect in asserting that examiner has not placed nay restriction on choice of variable B. In fact applicants were asked elect a group and a choice of variable B and applicants have not complied with that restriction requirement properly. However, in view of the election of species from the group elected, it is possible for the examiner to conduct proper prior art search.

4. Applicants argument that B-D-E-COOH is a common core is also not a tenable argument. As noted in the previous office action, except for COOH, all other groups namely B, D, and E are varible groups.

5. As for election species argument, strictly speaking claim 10 is only species claim and examiner could examine that speices and closely related species with the same core. Since applicants are offered to elect form different core groups,

examiner pointed to examples which by itself does not render the restriction requirement as improper.

6. As for sterioisomer issue raised by the applicant, it is not relevant as they have the same core and expect to share the same utility.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 a and 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. Recitation of the term "generalized formula" in claim 1 renders the claim indefinite, as it is not clear what is intended. Note term "generalized" implies more than what is being positively recited therein. Its deletion is suggested.

   Also note "of" is missing after "compounds" in this claim. See also claims 2 and 4.

   The same applies to the term "general" recited in claim 3, 5-6, and 9.

2. The method of use claim 1 also lacks therapeutically effective amount.

3. The last line of claim 1 appears to indicate a composition as it recites "and pharmaceutically acceptable salts and prodrugs thereof". Note Markush choices should be in alternate form. Also note the use plural in the claim implies more than one compound, more than on salt etc.

4. Recitation of the term "comprising " or "comprises" in the definition of variable group at various places in claim 1 renders the claim indefinite as the transitional phrase 'containing" is open-ended and can include more than what is being positively recited therein. See MPEP 2111.03 which states: The transitional term "comprising", which is synonymous with "including," "containing," or"characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., Genentech, Inc. v. Chiron Corp., 112 F.3d 495,501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

5. In claim 1, recitation of the term "prodrug' is deemed as indefinite. Prodrugs in general and as noted in specification, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various varible groups (see Q) include such groups, namely esters, amides, alkoxycaronyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug groups. Thus the term creates ambiguity.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cerebral diseases, does not reasonably provide enablement for prevention of cerebral diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant compounds are disclosed to have metalloprotease activity and it is recited that the instant compounds are useful, besides in 'treating, also preventing' cerebral diseases, for which applicants provide no competent evidence. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with cerebral diseases claimed herein. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'preventive' effect solely based on the metalloprotease activity disclosed for the compounds. Note substantiation

of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention:

The instant method of use claims are drawn to, besides treatment of cerebral diseases, prevention of cerebral diseases due to metalloprotease. However, specification provides no support for preventing cerebral diseases. Specification has not provided any evidence or nexus that because of the mode of action of the instant compound viz. metalloprotease activity, the compound would be useful for preventing cerebral diseases.

2) The state of the prior art:

There are no known compounds of similar structure, which have been demonstrated shown to be useful for preventing cerebral diseases. Furthermore, the prior art search in the related area does not suggest that because of the

mode of action of a compound, as metalloprotease inhibitor would be useful for preventing cerebral diseases.

3) The predictability or lack thereof in the art:

As noted above, although there several prior art which teach similar compounds as metalloprotease inhibitors, they do not teach use of the compound disclosed for preventing cerebral diseases and hence there is no art predictability or assurance that instant compound would do so. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present:

Specification provides no guidance or direction, as to how would one use the instant compound to treat or prevent all or any disorder.

5) The presence or absence of working examples:

There are working examples to show that how the instant compound could be used to treat or prevent disorders wherein metalloprotease is implicated as causative agent.

6.The breadth of the claim:

The breadth of the claim is broad enough to include treatment and prevention of cerebral diseases for which there is no pharmacological basis or showing in the specification.

7) The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Scott et al. WO 97/43240.

Scott et al. teaches several biaryl-oxobutyric acids as metalloprotease inhibitors, which include compounds claimed in the instant claims for the treatment of demylelating disease of the central nervous system. See pages 9-12 for summary of the invention, pages 13-23 for detailed description of the invention, including formula L on page 13, which corresponds to instant generic compound and page 24 for compounds made. See also pages 33-46 for examples of the compound made and the testing of the compounds as metalloprotease inhibitors.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Wolanin et al. WO 97/43247.

Wolanin et al. teaches several metalloprotease inhibitors, which include compounds claimed in the instant claims for the treatment of demylelating disease of the central nervous system and aneurismal disease. See pages 9-12 for summary of the invention, including formula L on page 10, which corresponds to instant generic compound, pages 13-31 for detailed description of the invention, and pages 31-54 for compounds, including Table I on page 38, made. See also pages 55-56 for examples of the testing of the compounds as metalloprotease inhibitors.

Claim 1-10 and 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Zandt et al. WO 97/43247.

Van Zandt et al. teaches several metalloprotease inhibitors, which include compounds claimed in the instant claims for the treatment of demylelating disease of the central nervous system, aneurismal disease, thrombosis and tumor metastasis. See pages 10-13 for summary of the invention, including formula L on page 11, which corresponds to instant generic compound, pages 14-23 for detailed description of the invention, particularly note the definition of R^{40} which includes groups claimed for instant R^6. See pages 24-26 for preferred compounds. See pages 45-62 for examples of compounds made especially see Table 1. See also pages 62-68 for examples of the testing of the compounds as metalloprotease inhibitors.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Bocan et al. WO 98/26773.

Bocan et al. teaches several metalloprotease inhibitors, which include compounds claimed in the instant claims for the treatment of neurological diseases. See formula shown on page 3 and note the definition of various variable groups. See pages 21-30 for preferred compounds. See entire document for method of use process of making and compounds made and testing of the compounds as metalloprotease inhibitors.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Purchase et al. WO 98/09940.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kluender et al. WO 96/15096.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kluender et al. WO 98/22436.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Dixon et al. WO 97/43245.

Each of the above four references teaches metalloprotease inhibitors bearing the biphenyl–4-oxo or 4-hydroxy-butyric acid for treating diseases which include neurological diseases. Each case see entire document.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Zandt et al. WO 97/43247.

Teachings of Van Zandt et al. as discussed in the above 102 rejection is incorporated herein.

Instant claims require variously substituted biaryl-butyric acids.

Van Zandt et al. teaches the equivalency of exemplified compounds with various substituents with that claimed. See pages 10-23, especially the definitions of various varible groups. Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in biphenyl ring and the and the side chain as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Scott et al. WO 97/43240 or Wolanin et al. WO 97/43247 or Bocan et al. WO 98/26773 or

Purchase et al. WO 98/09940 or Kluender et al. WO 96/15096 or Kluender et al. WO 98/22436 or y Dixon et al. WO 97/43245.

Teachings of by Scott et al. WO 97/43240, or Wolanin et al. WO 97/43247 or Bocan et al. WO 98/26773 or Purchase et al. WO 98/09940 or Kluender et al. WO 96/15096 or Kluender et al. WO 98/22436 or y Dixon et al. WO 97/43245 as discussed in the above 102 rejection is incorporated herein.

Instant claims require variously substituted biaryl-butyric acids.

Each of the above documents teaches the equivalency exemplified compounds with various substituents with that claimed in the definitions of various variable groups. Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in biphenyl ring and the and the side chain as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

10/17/2002